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ABSTRACT

This report provides an overview of research activities and needs in the area of contraceptive development. In a review of the present state, discussions are offered on the effectiveness and drawbacks of oral contraceptives, intrauterine devices, barrier methods, natural family planning, and sterilization. Methods of contraception that are in the experimental stage include regulation of male and female fertility and anti-fertility vaccines. Reports are given of research and clinical studies that are being carried out with the aim of improving barrier contraception, abstinence, and sterilization. A review is also presented of current research supported by the National Institute of Child Health and Human Development. Descriptions are given of future research needs for developing safe, effective, and convenient methods of contraception. These include needs for both clinical trials and laboratory research and further exploration of delivery systems for progestational and steroidal drugs and peptides. A section on resource requirements discusses aspects of product development and links between private and public health agencies, including administration of programs, fiscal matters, patent rights, and liability insurance. An appended bibliography contains 70 references. (JD)

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Contraceptive Development

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Contraceptive Development

I. Introduction

The primary objective of the contraceptive development program of the National Institute of Child Health and Human Development (NICHD) is to provide effective, safe, and acceptable means of contraception by developing new methods and improving the technology of fertility regulation. Research in this area has special features including the concerns of various population groups. Food and Drug Administration (FDA) regulations for clinical studies and eventual marketing of contraceptive products pertain to healthy individuals and are therefore uniquely different from those for therapeutics or prophylaxis. Differences in preclinical requirements, which are summarized in table 1, include long-term, multispecies animal studies. Constant surveillance in the course of research is necessary since elements of safety and efficacy are critical and can influence the development of technology at numerous points. In addition, research programs in contraceptive development are structured to accommodate the needs of a variety of users, including users of the natural family planning method. Data that summarize actual contraceptive practices as of 1976 are summarized in table 2. Research is also concerned with reducing the failure rate of different methods. Failure rates, which are presented in table 3, vary considerably and are influenced by the contraceptive intention of the user. Couples who wish to prevent an unwanted pregnancy have had, on the average, lower failure rates than couples who prefer to delay a wanted pregnancy.

The purpose of this report is to provide an overview of the activities and needs in research on contraceptive development. An examination of tables 2 and 3, for instance, indicates that oral contraceptives are used by a large segment of contraceptors and are highly effective, and

TABLE 1. Preclinical Requirements for Contraceptive Drugs

Preclinical Prerequisites	Contraceptives	Other Drugs
Clinical phase I	Ninety-day studies in rats, dogs, and monkeys must be completed prior to phase I studies, which involve 10 to 20 individuals for up to 10 days.	Phase I studies can be initiated after 2- to 4-week studies in two animal species.
Clinical phase II	One-year studies in rats, dogs, and monkeys must be completed prior to phase II studies, which involve approximately 50 women for three menstrual cycles.	Phase II studies can be initiated after 90-day studies in two animal species.
Clinical phase III	Two-year studies in rats, dogs, and monkeys must be completed and 7-year dog and 10-year monkey studies must be initiated before phase III testing may begin.	
New Drug Application (NDA)	Progress reports on long-term studies in dogs and monkeys are required at the time of NDA submission.	Chronic toxicity studies, including 1-year dog, 18-month mouse, and 2-year rat studies, completed by the time of NDA submission.

Source: Finkel, M.: Contraceptive regulation in the U.S. Paper presented at the PLACT Workshop on Developing Countries and the Regulation of Contraceptive Drugs and Devices, Seattle, Wash., July 24, 1978.

Goldenthal, E.I.: Current views on safety evaluation of drugs. FDA Papers May 1968: 13-18.

Goldenthal, E.I.: Contraceptives, estrogens, and progestogens: a new FDA policy on animal studies. FDA Papers November 1969: 15.

that barrier contraception and natural family planning have lower acceptability and relatively higher failure rates. The focus of research in these two areas would therefore be different. The emphasis in oral contraceptives, for example, would be on improving safety, whereas in the other areas, the emphasis would be on improving efficacy and acceptability.

TABLE 2. Trends in Contraceptive Practice in the United States 1965-1976

Participants Surveyed	1976	1973	1970	1965
		in thousands		
Married women age 15-44	27,185	26,646	25,577	24,710
(Unweighted N)	(6,414)	(7,566)	(5,884)	(4,810)
Contraceptive Practice	**1976**	**1973**	**1970**	**1965**
		by percent		
Using no contraception	32.2	30.3	34.9	36.1
Using contraception				
Wife sterilized	9.6	8.6	5.5	4.5
Husband sterilized	9.7	7.8	5.1	3.3
Pill	22.3	25.1	22.3	15.3
IUD	6.1	6.7	4.8	0.7
Diaphragm	2.9	2.4	3.7	6.3
Condom	7.2	9.4	9.2	14.0
Withdrawal	2.0	1.5	1.4	2.6
Foam	3.0	3.5	3.9	2.1
Natural family planning	3.4	2.8	4.1	6.9
Douche	0.7	0.6	2.1	3.3
Other	0.9	1.3	2.9	4.9
	67.8	69.7	65.0	63.9
Total	100.0	100.0	100.0	100.0

Source: Westhoff, C.F.: Trends in contraceptive practice: 1965-1973. Family Planning Perspectives 8: 54-57, 1976.

Ford, K.: Contraceptive practice in the United States, 1973-1976. Family Planning Perspectives 10: 264-269, 1978.

TABLE 3. Use-Effectiveness by Method in United States: Failure Rates per 100 Married Women, Age 15-44, in First Year of Use, 1970-1973

Method	Intention		Standardized
	Delay Birth	Prevent Birth	
Pill	2.0	2.0	2.0
IUD	5.6	2.9	4.2
Condom	13.7	6.6	10.1
Diaphragm	15.9	10.3	13.1
Spermicides only	16.7	13.1	14.9
Natural family planning	28.8	9.5	19.1

Source: Coleman, S. and Piotrow, P.T.: Spermicides--simplicity and safety are major assets. Popul. Rep. [H], Number 5, 1979. p. 91.

II. The Present State of Contraceptive Development

An Overview

Oral Contraceptives

The simplest way to improve an oral contraceptive (OC) preparation is to establish the lowest dose that continues to provide high efficacy without sacrificing control of the menstrual cycle. This objective has been achieved with the majority of preparations on the market and there is some evidence at present to suggest that low dosage forms of current preparations correlate with improved safety.[1,2]

Numerous attempts have been made to improve OCs by manipulating the combination of drugs. One of the earliest regimens involved the administration of estrogen followed by a progestin, in the belief that the sequence more precisely mimicked the hormonal cycle. Sequentials were subsequently withdrawn from the market, however, because of considerations for safety.[3] Another regimen was the progestin-only minipill, which was considered safer due to the total elimination of estrogens. Constant suppression of ovulation

is not a feature of this preparation, and it is believed that effects on the cervical mucosa and endometrium are significant aspects of its contraceptive efficacy. The preparation, however, has a somewhat lower efficacy and an occasionally inadequate cycle control. It is still available, but it does not have a major share of the OC market.[4]

More recently, two new approaches have been introduced. The tricyclic approach incorporates continuous administration of an OC over a three-cycle period. Its claimed advantage is that by eliminating two episodes of menses it produces temporary amenorrhea. Although initial clinical trials of this regimen were quite successful, there has been little effort to explore its acceptability and safety in large-scale clinical trials.[5] The triphasic approach involves subdivision of each cycle into three components of time during which the amounts of both the estrogen and progestin are varied. The total amount of estrogen ingested during the cycle is marginally increased, and the amount of progestin is significantly reduced. From the standpoint of efficacy and acceptability, preliminary trials of this regimen have been very encouraging. The preparation is marketed only in Europe.[6]

In actuality, currently available OCs are very effective, and it is unlikely that significantly more effective agents will be made available in the future. All of the available preparations, however, have been associated with undesirable side effects, and questions of safety have been raised. Research on new steroidal oral contraceptives has focused primarily on the synthesis of new progestins.

All of the combination OCs utilize either ethynyl estradiol (EE) or mestranol as the estrogenic component. The cyclopentyl ether of EE, a long-acting estrogen, has been extensively evaluated as a once-a-month preparation, but it has not become a marketed OC,[7] and research on new estrogenic components has been limited.

Because of the possibility of improved safety, several attempts have been made recently to substitute the "natural" estrogens estradiol (E_2) and estriol (E_3) for the synthetic hormones. In the preparations available for clinical trials, the dosages of both progestins and estrogens were quite high. The trials resulted in inadequate cycle control, however, characterized by excessive intermenstrual bleeding.[8]

Good animal models, which are currently in short supply, are essential to the development of safe OCs. Beagles, historically a species required in long-term safety studies, develop mammary tumors under the influence of certain progestins. As a result, a number of progesterone derivatives have been withdrawn from consideration as OC

components, although the appropriateness of this model has been questioned because of the unique sensitivity of the dog to progestins and the lack of similar adverse findings in human and other species.[9] Drug regulatory authorities in some countries no longer require the use of beagles for OC safety assessment. More recently, the question of progestin safety has been based on the effect of these agents on blood lipid profiles. Some progestins lower the content of high density lipoproteins and as a consequence possibly predispose the user to atherosclerosis. A cautious approach toward progestin-only contraceptives has resulted.[10]

Two questions have been raised with regard to the safety of estrogens. Of primary concern has been the relation of estrogens to the development of mammary and endometrial cancer. The progestin contained in combination OCs, however, apparently modulates this estrogenic effect.[3] Another question concerns the effect of estrogens on blood coagulability. Numerous studies have shown changes in blood factors related to coagulation under the influence of OCs, but there has been no direct evidence for predisposition to thrombosis.[11] The conclusion can be drawn that improvement in testing procedures, including large-scale clinical trials, may result in the development of safer drugs. The significant reduction in dosage of the currently available agents has been an important step toward this end.

Intrauterine Devices

The intrauterine device (IUD) has had a biphasic history of popularity. Its modern era started shortly after the introduction of oral contraceptives, and although its origins lie in antiquity, the mechanism of its contraceptive action is still not fully understood. Interference with gamete transport, changes in uterine environment, and interference with implantation are all known to contribute to its efficacy. The IUD gained popularity because it requires minimal motivation on the part of the user once it is placed in the uterine cavity. Its acceptability has been limited, however, as a result of such complications as perforation of the uterine wall, pelvic inflammatory disease, and pregnancy with the IUD in place. Bleeding, pain, ectopic pregnancy, and expulsion have also contributed to low acceptability and high dropout rates.[12]

Most of the early research focused on changes in the configuration of the IUD to improve uterine tolerance, and to produce less pain and bleeding and fewer expulsions. Although hundreds of configurations have been patented, relatively few are widely used.[12,13] Research on the IUD

has continued to focus on developing a configuration that is more compatible with the uterine environment. Even though there has been extensive work on device configuration, two of the earliest devices, the Lippes' Loop and Safety Coil, remain the mainstays of inert IUDs.

Because a configuration that is entirely compatible with the uterine environment is associated with lowered efficacy, research has also focused on developing bioactive devices that will alter this limitation and improve the overall performance of IUDs. Two main products have resulted: the progesterone-releasing device, Progestaset;[14] and two Cu-ion[15] releasing devices, the copper "T" and "7." They have been found to be highly effective. Although they cost more than inert devices and replacement is required periodically as the drug is exhausted, they offer the advantage of greater compatibility. The potential for developing IUDs that can release progestins over longer periods of time is high. Local action on the uterine environment and the small amount of drug needed to produce effective contraception are an advantage over the OC administration, for which a greater amount of the drug to produce an equivalent antifertility effect is needed.

Barrier Methods

Barrier methods of contraception, which have been available for many years, were the primary contraceptive modalities prior to the widespread use of OCs and IUDs.[16,17] Their main disadvantages have been their direct association with the coital act, their inconvenience, and their esthetic unattractiveness; but since numerous side effects of OCs and IUDs have been identified, interest in barrier methods has been renewed.[18] Aside from some minor problems associated with allergic reactions to rubber, few if any major health problems have been associated with the use of the diaphragm and the condom. During the past 2 years, interest in the cervical cap as a form of barrier contraception has increased. The overall status of vaginal contraception has been extensively reviewed in a recent publication.[19]

Efficacy rates for barrier contraceptives tend to vary considerably and depend on the correctness of their use and on the user's motivation. Failure rates for both the condom and the diaphragm in combination with spermicidal preparations have been low where client motivation has been high and instruction has been adequate.[20,21] Many studies, however, report relatively high failure rates in other circumstances.[22]

A diaphragm must be fitted by a doctor or a specially trained paraprofessional. Since the diaphragm itself may

not represent an adequate barrier to the passage of spermatozoa into the cervix, it is recommended that the method be used in conjunction with a spermicide and that it remain in the vagina for several hours after intercourse. The available spermicidal preparations, whether in the form of jellies or foams, are of limited duration and are often inconvenient to use. The efficacy of foaming spermicidal suppositories recently introduced as a more convenient preparation has not yet been proved.[23]

The condom is an effective contraceptive method used by about 10 percent of contraceptors. Its acceptability is restricted by the fact that it is directly associated with coitus, and care must be taken both in putting it on the penis prior to intercourse, and upon withdrawal. Some individuals also complain about the loss of sensitivity. Condoms are more widely used in other countries, such as England and Japan, than in the United States. The popularity elsewhere is attributed to cultural-educational differences, and, possibly, to a better quality product.[24]

Although the demand for the cervical cap has risen considerably during the past 2 years, primarily because of active promotion by women's health cooperatives, the device has not been used extensively to date. The cap fits snugly over the cervical opening and, depending on type, can be used with or without a spermicide. It can be left in place over longer periods of time than the diaphragm, and some hard plastic versions can be left in place throughout the whole intermenstrual period. Some women, however, find the cap difficult to insert and remove. In addition, the device cannot be fitted properly for some women because of cervical anatomy or pathology.[17]

Caps are not currently manufactured in the United States and must be imported. Because of limited data, the Food and Drug Administration still classifies the cervical cap as an experimental device.

Natural Family Planning—Periodic Abstinence

Methods of natural family planning (NFP) rely on the three distinct phases of the woman's cycle of fertility: (1) the preovulatory, infertile period; (2) the fertile period about the time of ovulation; and (3) the postovulatory, infertile period. The duration of these three phases is determined by the length of time spermatozoa (48-96 hours) and egg (24 hours) remain fertile. Unless pregnancy is desired, a couple practicing NFP must abstain from intercourse during the woman's fertile period.[25]

Natural family planning is based on the observation of bodily changes that occur during the menstrual cycle as a result of a fluctuating balance of reproductive hormones. During the preovulatory period, the cycle is dominated by the estrogens and, after ovulation, by progesterone. These hormones are produced in different parts of the ovary. Estrogens are produced predominantly by the follicles, and progesterone is produced by the corpus luteum, which is formed after the follicle ruptures. Under the influence of these hormones, body changes occur that women learn to recognize and use in managing their fertility. With the use of such physiological endpoints, predictions can be made of fertile periods that are more accurate than those of the older calendar rhythm method, which depended solely on calculations based on prior cycle lengths.

A concept inherent in the use of NFP for contraceptive purposes is abstinence during the fertile period. The criteria for defining the fertile period are physiologically sound, and specific adherence to the criteria results in effective fertility regulation.

The three most commonly used NFP methods are the basal body temperature (BBT) method, the cervical mucus or ovulation method (OM), and the symptothermal (ST) method. In the BBT method, women observe the rise in basal body temperature that occurs after ovulation as a result of increased production of progesterone. The postovulatory, infertile phase begins on the third night of rising temperature. To use the method successfully, a woman must take her temperature daily. Intercourse is restricted to the postovulatory, infertile period. In the cervical mucus or ovulation method the quantity and quality of cervical mucus are observed. When the ripening follicle begins to produce estrogens, the hormones stimulate mucus-producing glands in the cervix. A woman can detect the mucus that is produced. The appearance of mucus signals the beginning of the fertile period. The peak day is the last day of wet slippery mucus, and approximates the time of ovulation. The end of the fertile period occurs 4 days after the peak day. In the symptothermal method cervical mucus is used to determine the beginning of the fertile phase, and basal body temperature to define the end of the fertile phase. Couples practicing this method use additional endpoints to guide them in determining fertile and infertile phases of the woman's cycle.

In an assessment of NFP methods, it is important to distinguish between the methods themselves and compliance with the methods by users. Ample evidence clearly indicates that failure rates are very low (1-2 percent) when NFP methods are practiced correctly. Failure rates as high as 25 percent have been reported as a result of an inadequate understanding of the method or from deliberate risk-taking.[25-27]

Sterilization

During the past decade, sterilization has gained in popularity.[28,29] It is currently considered the world's leading method of contraception.[30] In the female, the procedure involves some form of tubal occlusion, which prevents fertilization by blocking the passage of both spermatozoa and ova. For the male, it involves occlusion of the vas deferens, which prevents release of spermatozoa during ejaculation. Clinically accepted methods of either tubal ligation or vasectomy require some form of surgery, but the procedures are relatively simple and both can be done on an outpatient basis. The negative aspect of these surgical approaches is their relative irreversibility. Although specific complications may arise as the result of the operations, postoperative morbidity and mortality have been low.

Both vasectomy and tubal ligation must currently be viewed as permanent contraceptive methods, and they are generally limited to individuals who no longer wish to have children. Surveys indicate that even among this population, the operations would be more attractive if they could be successfully reversed.[31] While surgical reversals of sterilization have been accomplished in both men and women,[32,33] the success of a surgical attempt to reverse sterilization of either sex depends almost entirely on the nature of the initial operation. Numerous approaches have been tried to make reversibility more successful, but they remain experimental.

Sterilization is a highly effective method of contraception for both the male and the female and, unlike all other methods, requires no further responsibility on the part of the user. It should be noted, however, that occasional failures have occurred as a result of surgical error or of recanalization.

Experimental Stages

Several methods of contraception are in the experimental stage. Most have been studied extensively in laboratory animals and in related clinical situations.

Regulation of Female Fertility

One new progestin, a chemical modification of an existing one, has been studied extensively during the past decade as a new component of OCs. Although clinical trials

on this preparation have shown high efficacy, its safety needs to be assessed.[34]

There has been considerable research on developing long-acting progestin formulations,[35] and initial efforts have focused on injectable preparations.

Depo-Provera™ has been used outside the United States as a contraceptive. It has been the subject of an ongoing safety controversy for a number of years, and it is available in this country only for treatment of gynecological disorders and some forms of cancer. Another long-acting preparation being studied contains a different progestational agent, norethindrone enanthate. Both preparations have exhibited high efficacy, but breakthrough bleeding has posed a major problem. Depo-Provera™ is effective for 3-6 months after a single injection. The other preparation is effective for 2-3 months.[36-39]

Another method under study involves a Silastic-based drug delivery system implanted under the skin that continuously and steadily releases the contraceptive drug by diffusion through the wall of the device. Considerable clinical experience has been accumulated with a variety of contraceptive progestins released from such subcutaneous reservoirs. The systems are attractive because they can function over extended periods of time (6 months or longer). The primary difficulty has been breakthrough bleeding. Also, the device must be surgically removed when the drug is depleted.[40-42]

It has been found that membranes capable of controlling drug release can be made of biodegradable polymers that are absorbed in the body after drug release is completed. Polylactide systems have been studied extensively and have the potential of being made into microcapsules that can be administered by injection rather than implantation. Another experimental drug delivery system operates on the principle of erosion of the polymer matrix into which the drug is incorporated. Both the diffusion and bioerosion systems have produced very steady blood drug-levels over prolonged periods of time. The amounts of drugs needed to produce a contraceptive effect are greatly reduced when administered by means of implanted drug delivery systems.[43]

Ready absorption of steroidal drugs through the vagina permits utilization of natural steroids that are relatively inactive by the oral route. To take advantage of this fact, researchers have fashioned Silastic vaginal rings that fit over the cervix and release contraceptive drugs. Menstrual-like bleeding is produced on a cyclical basis similar to that following OC use on a monthly basis. The rings are easily removed, and the same ring can be reused for a number of months. Additional research is needed on the safety and acceptability of vaginal rings.[44]

As mentioned previously, research on the IUD has focused on the development of devices that can release a variety of drugs, the effect of which is to reduce pain and bleeding. The primary thrust is improved acceptability as opposed to improved efficacy.

Barrier Contraception

Current research is focused on the development of improved diaphragms and different methods of spermicide application. Attention is directed toward new materials, such as sponges, that may make insertion in the vagina less of a problem, allow for a longer retention time, and, to a degree, disassociate the device from the coital act. A new kind of custom-fitted cervical cap that can be worn for extended periods of time is also being studied. The cap has a one-way valve permitting the exit of menstrual fluid. More information is needed for proper evaluation of the concept. Research is also being done on improved spermicidal formulations. A longer acting, more convenient formulation would improve their acceptability.

Regulation of Male Fertility

Numerous attempts have been made to develop a drug or combination of drugs, similar in concept to OCs for women, that produces male infertility in a predictable fashion. Most of the focus has been on the use of androgens (male sex hormones) or on progestational drugs in combination with androgens. From the numerous trials that have been conducted, it is evident that complete suppression of sperm production (azoospermia) is yet to be achieved consistently. The time needed for suppression varies considerably in different men and ranges from several weeks to several months.[45-47] While total sperm suppression is recognized as a desirable goal, there is considerable disagreement on how far the sperm count must be depressed before reliable infertility is achieved. It has been reported that men whose sperm count has been drastically reduced as a result of experimental contraceptive treatment have maintained fertility.[48] In addition, what constitutes an acceptable failure rate is an unresolved issue.

Publicity was recently generated by the discovery in China that gossypol, a chemical obtained from cottonseeds, can induce infertility in the human male. The chemical has undesirable medical side effects, however, and in large doses is quite toxic. Animal research studies in the United States have confirmed its antispermatogenic activity as well as its toxic manifestations.[49-51]

Antifertility Vaccines

Much attention has recently been given to immune approaches to the management of fertility. Animals immunized with a variety of antigens of reproductive origin have been rendered infertile. Antibodies to a number of reproductive hormones have been produced that have also rendered animals infertile. In addition to experimentally induced immunological infertility, there are naturally occurring infertile conditions that may have an immunological basis.[52,53]

In the absence of a known highly specific antigen that can be used for immunization, a practical antifertility vaccine has not yet been developed. It is important to have an antigen to which antibodies will be highly specific, i.e., interfere with a selected process and not affect other functions. Difficulties arise in the selection of proper antigens, the preparation of formulations to induce good antibody response, and the determination of safety.

The most widely investigated vaccine is based on a derivative of human chorionic gonadotropin (HCG). The scientific basis for this preparation was the presumed specificity of HCG and the ability of antibodies to a fragment of this hormone to prevent pregnancy. Problems with this vaccine stem from its low antigenicity and the inconsistent titer of antibodies following vaccination. High antibody titers are needed to prevent pregnancy. Secondary problems related to nonspecificity of HCG have also been raised, especially in terms of possible safety.[54,55]

Vaccines that result in spermatogenic arrest have also been produced. They are based on neutralization of the follicle-stimulating hormone (FSH), which is believed to be necessary for spermatogenesis. Clinical experience with these vaccines is limited.

Development of a vaccine based on unique antigens in the egg (zona pellucida) and the sperm is the subject of current basic research interest.[56,57] Immunological control of fertility remains a potentially viable area, and considerable basic scientific research is needed before applied research and development programs can be reinitiated.

Periodic Abstinence

Careful clinical studies that attempt to pinpoint ovulation based on hormonal determinations, observations of cervical mucus, and basal body temperature, indicate a close relation between the various indicators of the female's

fertile period. Differences among the various endpoints, however, do occur, and they contribute to unnecessarily prolonged periods of abstinence. Researchers are attempting to simplify the technology of hormone determinations in readily accessible body fluids, such as urine.[58,59]

Efforts are also being made to identify endpoints other than hormones that can accurately predict the status of the menstrual cycle. The sophisticated technology that is available has not yet been packaged for home use.

Sterilization

As mentioned previously, it has been recognized for some time that sterilization in both men and women would be made more acceptable if it were more easily reversible. To this end, a variety of approaches have been attempted in both sexes. In the male, the approach focused on placing some form of reversible valve in the vas deferens. The approach appeared to be quite simple, but after several years of intensive research it was abandoned because of the failure of the implants to block sperm passage completely.

In the female, attempts were made to block the uterotubal junction with a variety of metal or plastic plugs. Results of these approaches have also been negative. The only approach on which clinical research is continuing involves the hysteroscopic instillation of liquid Silastic into the tubal opening. In the presence of a catalyst, the Silastic cures within the tube to produce a solid plug. In animal experiments, removal of the plug with subsequent restoration of fertility has been accomplished. It is not known whether uncomplicated retrieval of the plug can be accomplished in women.

Several methods have been attempted to produce nonsurgical tubal occlusion. All of them involve uterine instillation of chemicals which, by means of necrosis of tubal epithelium, can produce tubal blockage. Problems have been encountered with many agents, primarily in a failure to produce complete occlusion. However, research on this approach to sterilization continues to attract attention.

Review of Current Research Supported by the NICHD

Three clinical trials to assess the potential of analogs of the hypothalamic hormone called LHRH (luteinizing hormone releasing hormone) as fertility-regulating agents

are currently in progress. A fourth study, involving a new, untested analog, is being finalized. These trials will attempt to analyze superactive agonists in both the male and female. Background clinical information suggests that suppression of ovulation and disruption of progesterone production can be attained with the agonists, but strategies must be devised to prevent major perturbations of the menstrual cycle.

Although the antifertility effect of the agonists has been achieved in laboratory animals, it is yet to be demonstrated in the human male. Because the spermatogenic cycle in the human male is quite long (74 days), the agonists will have to be administered for extended periods of time. If the agent stops sperm production, it is also likely to reduce production of the male sex hormone, testosterone, which may cause loss of libido and require substitution therapy. Studies in both the male and the female represent the first stage (phase I) of clinical investigation to establish the safety of these drugs, to be followed by much more extensive studies on efficacy. The initial trials will provide information on the practical value of these drugs.

Two additional drug delivery systems have been approved for clinical studies. The objective of one is to provide for continuous, steady, slow release of the progestin, norgestrel, from a subcutaneous implant of caprolactone polymer. Preliminary animal studies have revealed no potential problems, and this system will be evaluated in a small number of women to ensure that it does not cause irritation or have other undesirable side effects. The other drug delivery system, which uses an oral formulation, seeks to reduce the initial peak of absorption and prolong the absorption period, and should result in a more sustained blood level of contraceptive drugs. It is hoped that by reducing the high initial peak and extending the period of absorption, the safety of currently available contraceptive drugs can be improved.

Another major area of clinical activity involves the evaluation of new barrier methods of contraception. A comparative, randomized, clinical trial of a vaginal contraceptive suppository (Encare-Oval™) and the diaphragm will be completed in about 1 year. Preliminary data indicate that the suppository is an effective contraceptive method. Because of side effects, however, there are indications that its acceptability and rate of continued use are not satisfactory. Use-effectiveness studies of a disposable sponge diaphragm are also being initiated. A spermicide will be incorporated into the sponge, which may then be left in the vagina for 24-48 hours. The use-effectiveness, acceptability, and continuation rates for this device will be compared with those of currently available diaphragms.

Finally, additional studies involving cervical caps are being implemented.

Among research activities in progress, one approach centers on the synthesis and testing of new compounds--particularly the synthesis of antagonists to the hormone LHRH. Since normal reproductive function depends on the synthesis and release of LHRH from the hypothalamus, it is reasonable to expect that antagonists of this hormone will produce an antifertility effect. Numerous peptides (amino acid chains) with antagonistic properties have been synthesized and have been demonstrated to have the desired properties. These antagonists have recently been found to be sufficiently potent to warrant full-scale toxicological assessment and initial clinical trials.

Other areas of synthesis that have yielded potentially useful leads include prostaglandins, androgens, and estrogens. Research on prostaglandins focuses on compounds that can disrupt corpus luteum function and the synthesis of progesterone. Androgen synthesis has yielded very potent compounds with prolonged activity, and in combination with other drugs, may prove useful in male contraceptive regimens under circumstances where libido is impaired, to achieve more complete sperm suppression. Interest in estrogens stems from their presence in OCs that combine an estrogen and a progestin to achieve the needed contraception. Many of the reported side effects have been attributed to estrogens and, more specifically, to ethynyl estradiol, which is the predominant estrogen used in OCs. Estrogens that are active orally and different structurally from ethynyl estradiol may prove to be of value as contraceptive agents.

The contraceptive development program benefits from the availability of a biological testing capacity, which includes a sizable nonhuman primate colony. The program also maintains a synthesis facility that supplies a variety of chemicals unavailable from other sources. The biological testing program not only serves as an adjunct to the synthesis activities, but also makes it possible to evaluate drugs originating elsewhere.

Two drug delivery systems will be explored in human volunteers in clinical research. One is based on a bioerodable polymer and has already been tested in a small number of volunteers under the auspices of the World Health Organization (WHO). Current research focuses on the incorporation of a different drug into the polymer matrix and on its in vitro and in vivo release. In another project, an attempt is being made to synthesize a different bioerodable polymer that may be easier to synthesize and manipulate in terms of drug release. Clinical evaluation of this polymer as a delivery system is still 1 to 2 years away. Systems previously considered for subcutaneous drug administration all

require minor surgery for implantation. While this consideration may be somewhat of a drawback, such systems afford the opportunity of retrieval if there is a medically indicated need. Delivery systems in which the drug can be injected with a syringe simplify the method of administration. Several systems based on microencapsulation of contraceptive drugs have been developed, and relatively stable drug release rates have been accomplished in animal studies. Additional studies dealing with manufacturing technology and release rates are in progress.

Efforts to computerize interpretation of menstrual cycle data relating to the practice of natural family planning are continuing. Availability of computer programs permits instructors to identify problems more efficiently and thus improve client-instructor interactions. A comparative, randomized study of the ovulation and symptothermic methods of NFP has been completed.[26] This was the first attempt to conduct a randomized efficacy study involving methods of periodic abstinence, and its basic conclusions appear to be substantiated by other studies. The study has generated considerable data on a variety of topics of importance to NFP. An effort is now underway to analyze the data on the respective methods and to focus on the elements that enhance their use. Additional work is in progress to devise immunochemical methods to pinpoint ovulation more precisely.

III. Future Research Objectives

Introduction

Although there have been advances in technology since the initiation of the contraceptive development program by the NICHD in 1969, a very real need for better methods of fertility regulation still exists. Consumers are demanding safe, efficacious, and convenient methods of contraception, and the demand can be met only by means of intensive research and development programs.

The Greep report,[60] the House Select Committee on Population,[61] and the Population Council[62] have all made urgent pleas for expansion of studies on basic human reproduction and fertility regulation. Numerous research areas have been identified as worthy of exploration. There are potentially promising areas that should be explored as the result of advances made in basic research.

An important aspect of contraceptive development is the interaction and interdependence of applied product development research and basic research. An applied program that

supports contract research should also support research that is directed toward a better understanding of reproductive processes in the male and the female, especially with respect to the influences of various drugs on body processes. Better understanding of the functions of the reproductive system in fertile and infertile states can result in more practical therapies, especially therapies based on hormonal analogs.

The newer experimental approaches based on the hypothalamic-releasing factors are but one example where drug development is very much dependent on basic research and understanding of clinical endocrinology and the influence that these chemical entities have on reproduction. Such a multifaceted approach may discover the potential use of drugs not only as contraceptive agents but also as therapeutic entities for a variety of disorders. As a prerequisite for the development of safer drugs and also a tool for eliminating drugs that may be potentially harmful, an applied program in contraceptive development should support basic research that is crucial to the better understanding of drug action.

The difficulty that has thus far been experienced in the development of an effective male contraceptive agent can be explained in part by a lack of understanding of male reproduction, particularly by a lack of precise knowledge of hormonal interactions that are responsible for sperm production. What are the roles played by the various reproductive hormones in maintenance of spermatogenesis? A variety of substances that may render the male infertile should be screened. The effort should be coupled with intensive investigations into the science of andrology, which encompasses all of the elements of male reproduction. It is likely that such a dual approach will lead in time to the development of useful male contraceptives.

Numerous regulators of ovarian and testicular functions that have been isolated in impure form should be purified, analyzed for chemical composition, and eventually synthesized. In this area of research, basic and applied research can advance hand in hand. As a new understanding develops of the role that these factors play in ovarian and testicular function, the implications can be explored in a more applied fashion.

Clinical Trials

LHRH Analogs

Clinical trials currently in progress are intended to assess the potential safety and utility of the LHRH analogs as several contraceptive modes. These trials, involving a

relatively small number of individuals, should be completed during the next 2 to 3 years. If the contraceptive potential of the LHRH analogs for both the male and female is established, wider trials involving more volunteers will be needed to make a preliminary assessment of efficacy.

Clinical research in the male should be expanded in order to establish the full potential of the LHRH agonists. There is a need for studies involving different dose schedules before contraceptive trials can be contemplated. Because sperm production is a continuous process and its suppression can be accomplished only with continuous drug administration, new routes of drug administration are necessary. While daily injections of drugs may be tolerated in a controlled clinical trial with highly motivated volunteers, such an approach does not work in practice. If the initial trials demonstrate that the agonists have a potential as male contraceptives, research and development programs on new methods of drug administration will need to be established.

Most current clinical research on LHRH is focused on the synthetic analogs with agonistic activity (agonists). Considerable research, however, has been undertaken on the synthesis of analogs with antagonistic activity (antagonists). The use of drugs that antagonize the action of natural hormones is well-established in numerous areas of therapeutics. In both laboratory animals and humans, LHRH antagonists have been demonstrated to antagonize normal reproductive function. The studies have been somewhat limited, however, by the relatively low potency of the antagonists and by the concomitant need to administer large quantities. During the past years, chemists have been successful in synthesizing more potent antagonists, and this area of research is ready for extensive clinical exploration. Before these more potent drugs are tested in the human, however, they must be evaluated for safety in animals.

Barrier Methods

Several clinical trials have recently been initiated on the efficacy of different vaginal barrier methods. Studies involving the cervical cap and the sponge diaphragm may provide enough information for the private sector to start marketing the devices within the next 3 years.

Drug Delivery Systems

The objective of the research on drug delivery systems is to determine the lowest dose of a drug that produces the desired antifertility effect.

The implantable caprolactone delivery system for progestins is in the first stages of clinical experimentation (phase I). If the initial data are satisfactory, studies through successive clinical stages and ultimately efficacy trials (phase III) will be needed. Testing of an implantable drug delivery system is quite complex, especially if delivery devices disintegrate in the body and cannot be removed. This and similar systems will require increased clinical testing, particularly in regard to close monitoring of body functions.

One of two bioerodable implant systems should be ready for clinical trials within a year; the other should be ready within the next several years. Both can achieve steady, prolonged release of contraceptive drugs. Since these systems are classified as drugs, in addition to the contraceptive drugs that they release, they will require long-term animal safety studies. The actual duration of such studies may depend on the nature of the animal models that are available and useful for safety assessment.

Studies of a long-acting injectable system comprising a microencapsulated drug should be initiated. Injection should simplify the administration of this drug delivery system and make it more acceptable to the public.

Clinical phase I trials of a new delivery system of existing oral contraceptive drugs should be completed soon. Because the specific contraceptive drugs and chemical components of the system are currently being used by the public, there are minimal requirements for animal safety studies. Clinical trials should proceed on a schedule similar to that for testing an oral contraceptive. A careful assessment will have to be made on whether the anticipated changes in intestinal absorption result in improved safety. If this form of OC administration is found to improve the safety of existing OCs, it could result in improved acceptability of existing drugs. The chemical metabolism of volunteers using this system clinically will have to be compared with that of volunteers using conventional OCs of the same composition. Developments in this area should proceed with private sector involvement at a relatively early stage.

The NICHD-sponsored program has had close cooperation with the WHO program on human reproduction in the field of drug delivery systems. Cost sharing on one project has been in effect for the past 2 years and is expected to continue. The clinical research network that the WHO has established in both developed and less developed countries could play an active role in development of drug delivery systems.

Injectable Long-Acting Progestins

Since the long-acting injectable progestin, Depo-Provera™, faced an uncertain marketing future in the United States, clinical studies of another progestin, norethindrone enanthate, were undertaken. Considerable experience with this drug was available from clinical trials conducted by the drug company and by WHO. Small-scale (phase I) clinical trials have been completed in the United States. Projections for expanded phases II and III in the United States have been completed, and multiclinic, 2-year trials have been initiated outside this country by the WHO. These trials should provide information on the efficacy and safety of norethindrone enanthate.

In addition, the NICHD in cooperation with the WHO has participated in a screening program for long-acting progestins. The objective of this program has been to develop a drug that would be a viable alternative to either Depo-Provera™ or norethindrone enanthate.

Natural Family Planning

Attempts are being made by several research groups to devise better methods for determining the fertile period; some of these endeavors may require future clinical trials.

Utilization of Natural Estrogens

Estradiol, a naturally occurring hormone, is being evaluated as a component of OCs. Using the results of clinical trials that have been conducted abroad, these studies are based on the premise that the natural hormone is likely to be safer than the synthetic estrogens currently used in OCs. The initial trials focus on the issues of cycle control and clinical chemistry, and if they show promise, a more extensive research and development program may be warranted.

Laboratory Research

Synthesis

The synthesis program relies heavily on the availability of chemical leads, which originate from identification of natural substances with contraceptive potential, screening programs of available chemicals, or specific synthesis

programs based on information of drug receptor interactions. While the 1950s and 1960s were characterized by intensive synthesis in the steroid area, there was a reduction in steriod synthesis in the 1970s and an increase in the synthesis of contraceptive peptides, particularly LHRH.

Basic research has identified the presence of other regulators of reproductive function in the ovaries and in the testes. One of them, the peptidic regulator, has been found in follicular fluid surrounding the egg; this material has been called folliculostatin or inhibin. Although considerable biological and biochemical research has been undertaken to characterize this substance, its precise nature is yet to be identified. Biological experiments with crude preparations have shown that the substance has considerable potential for management of fertility, but a synthesis program must await its identification. The isolation, purification, and identification of this substance is therefore essential. Experience with the LHRH program should prove invaluable to efforts in this area. In addition to folliculostatin, other naturally occurring substances in the ovaries and testes need to be characterized, including an LHRH-like substance that is present in the ovaries.

Interference with the production and(or) action of progesterone has been the goal of numerous synthetic programs. While good antiestrogens and antiandrogens have been synthesized, little progress has been made in synthesizing a useful antiprogestin. Several lead compounds have been identified but have not resulted in successful development of useful antiprogestins.

Another possible area of synthesis that needs to be explored is based on the discovery that gossypol, a chemical found in cottonseeds, can render the male infertile. Since gossypol given alone may pose a health hazard, it is essential to neutralize its undesirable properties.

Synthesis Facility

During the past several years, the NICHD-supported synthesis facility has provided custom synthesis of numerous chemicals and has helped with the synthesis of key intermediates. Pure gossypol, for example, was recently analyzed. The availability of this facility should be maintained.

Biological Testing Facility

The biological testing facility, which has been in existence since 1972, conducts primary biological screening

and advanced biological studies on drugs originating both from the NICHD program and from outside sources. It has made an accurate, unbiased comparison and assessment of several drugs originating from different sources. The collaborative program involving the NICHD and WHO, which has as its objective the synthesis of long-acting progestins and androgens, depends on this facility for biological evaluation. The overall capabilities of the testing program have been extended to include a sizable colony of monkeys.

Drug Delivery Systems

A number of projects on drug delivery systems have reached the stage of clinical trials. Systems for delivery of progestational drugs have been developed, and the overall laboratory phase should be completed during the next 2 to 3 years. While it is unlikely that any additional studies on the delivery of steroidal drugs will be initiated, drug delivery systems for peptides will need to be devised.

Barrier Contraception

For the next 2 to 3 years research that has already been initiated to develop improved barrier contraceptives should be continued in order to begin clinical trials. All these efforts are still oriented toward the female user. By improving the ease of insertion of either the diaphragm or the cervical cap, these devices may become more acceptable. Studies on new spermicidal barriers and spermicidal materials incorporated into the matrix of the diaphragm or cap are in progress.

Reagent Supply Program

The reproductive research community depends heavily on a supply of high-quality, standardized reagents. Many of these reagents cannot be procured from commercial suppliers and have to be prepared by experts working in a specific area. On occasion, some of the reagents are by-products of projects that are directed to other purposes. It is difficult to measure the contribution that this program makes toward the overall research endeavor. Hundreds of researchers in the United States and abroad, however, avail themselves of this supply. Moreover, the materials are produced in relatively large quantities at considerable savings in cost.

Distribution of the material is under the auspices of the National Pituitary Agency which was established by the National Institute of Arthritis, Metabolism, and Digestive Diseases. The NICHD has supplied the Agency with HCG, its subunits, and antisera, which are used for early diagnosis of pregnancy and other research endeavors. Cut off in the supply of HCG would have a very adverse effect on research. Monkey pregnancy diagnosis kits supplied by the NICHD have been of great value in breeding programs that provide nonhuman primates for research as well as in breeding of certain endangered species. In a similar vein radioimmunoassay reagents for nonhuman primate gonadotropins permit closer monitoring of primate reproduction and lead to a better understanding of both basic and applied research endeavors.

In addition to the above reagents, the program continues to supply small and large samples of the hypothalamic hormone LHRH. More recently sizable quantities of follicular fluid that researchers are using as the source of other biologically important substances have been procured and distributed to the scientific community. These substances appear to regulate follicle and ovum growth and offer a future generation of fertility regulating agents. The program relieves individual researchers of the burden of trying to obtain it from local slaughter houses.

It is recommended that this program be maintained and be expanded as new preparations are made available.

Coordination and Collaboration

The development of improved fertility-regulating methods is the primary objective of several existing public programs. They receive funding from several sources: primarily the U.S. Government, as is the case with the NICHD and the Agency for International Development (AID); private foundations, such as the Ford, Rockefeller, and Mellon Foundations; or, as in the case of the WHO program, foreign governments. Sustained and improved program interactions between organizations and agencies should be encouraged.

In addition, collaboration of two or more programs that have an interest in similar technology can result in considerable savings. When circumstances preclude joint funding, support for different aspects of a single research project can be coordinated. The NICHD has collaborated in domestic programs as well as with the WHO. The results have been productive, and such joint efforts must continue. Although different parts of the world show different levels of concern for fertility regulation, the technology should be

shared on a global basis and should generate wide-scale benefits. Interactions with scientists in other countries through officially established channels should also be encouraged.

Additional Considerations

As previously indicated, research on improving IUDs is needed. Although advances have resulted from the introduction of the "bioactive" IUD, the progesterone-releasing IUD, and the copper IUD, research thus far on shape and on new materials for IUDs has been much less productive. Development of IUDs that would decrease pain and bleeding would be considered a major advance.

The world's folk and scientific literature refers to a number of plant preparations that have been used by native populations to control their fertility, but specific documentation of the precise nature of the antifertility effect is often not available. Proper exploration of the antifertility potential of plant preparations is a difficult, expensive, and time-consuming task. The WHO has initiated a plant-screening program in a number of less developed countries. The WHO findings and resources might be useful in further exploration of plant preparations for regulating fertility.

Antifertility vaccines are another prominent area of research. Development of vaccines is a complex issue, and their scientific base in regulating fertility has not yet been established. While some basic research in this area is supported by the NICHD, there has been no organized approach. The NICHD has supplied reagents used by scientists in vaccine development based on human chorionic gonadotropin. Two organizations, the WHO and the Population Council, are actively involved in this research area. Future research may yield information that will open up a need for an organized research effort.

IV. Resource Requirements

Unique Aspects of Product Development: The Public-Private Sector Link

The complex nature of product development must be considered in the development of new contraceptives. This

is particularly true for public sector agencies, such as the National Institutes of Health (NIH), that support research conducted by private sector organizations. In this endeavor, it is important that costs be shifted from the public to the private sector. This shift can take the form of a total technology transfer to the private sector, or as an alternative, to cost-sharing contractual arrangements. It appears that the wider the potential utilization of a specific drug or device, the more likely it is that adequate private support for continuation of the developmental process can be secured. (See figures 1[63] and 2[64] for additional information on the drug development process and relative costs.)

It should be mentioned in this connection that the pharmaceutical industry was very active in contraceptive development in the 1950s and into the mid-1960s, but that in recent years its interest has dwindled.[65]

Administrative Matters

Procurement regulations are such that the time needed for the development of a new product is often quite lengthy. The procurement process is based on soliciting the widest competition possible, and the product development process frequently turns on factors outside the agency. Unanticipated problems with a drug or device, for example, can require a major alteration in strategy.

In addition, the phases of a Government project, unlike those of a pharmaceutical company, are undertaken by different institutions and agencies. A new drug, for instance, can be synthesized in an academic environment, and biological evaluation, animal safety studies, and clinical studies can be separately undertaken by hospitals and other facilities. Coordination of the various phases of a project can therefore become a major administrative obligation. There is a crucial need to clarify the roles that are played in this process by the various segments of the scientific and industrial communities.

Fiscal Matters

The development of new pharmaceutical products is costly. Some estimates for putting a new drug on the market have reached $54 million.[66] Although costs can be distributed over a period of several years, it is difficult to maintain advanced-stage testing of several drugs or devices without a distribution of costs between the public and

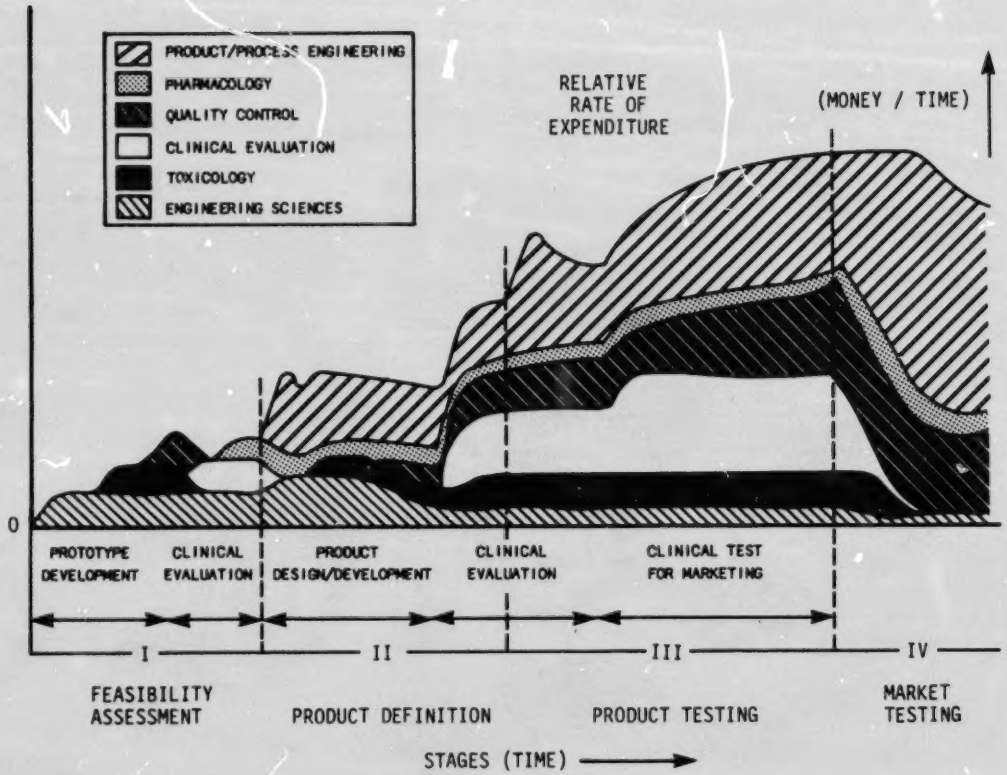

FIGURE 1. The relative costs associated with stages of medical product development[63]

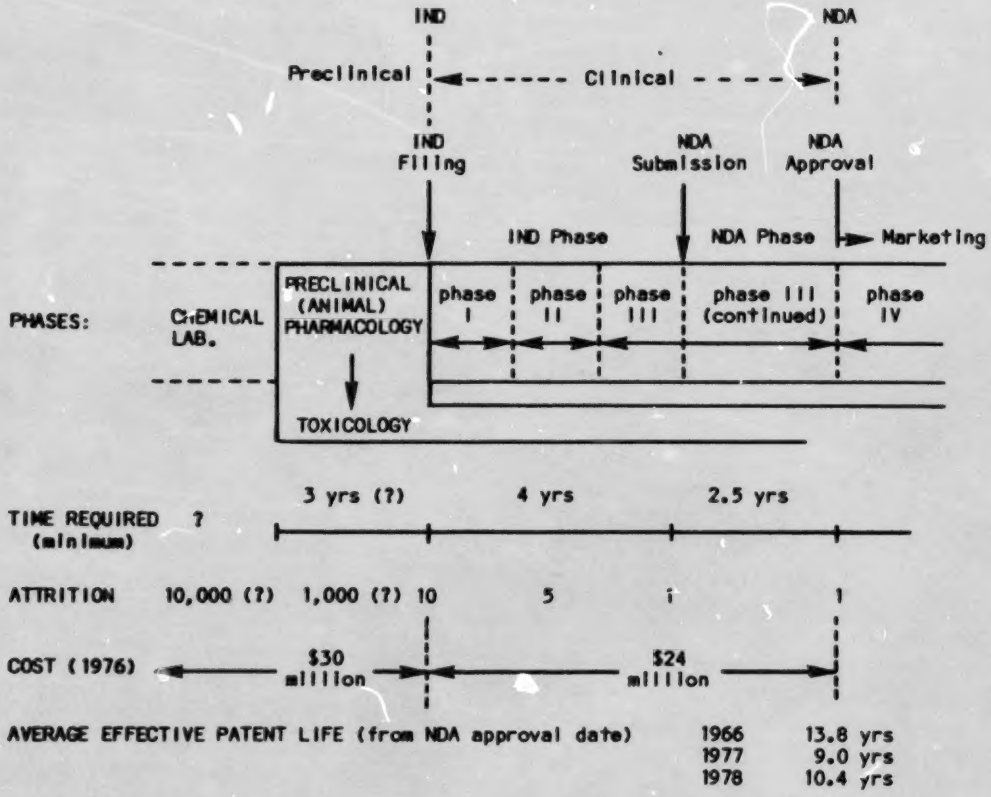

FIGURE 2. Drug development in the United States[64]

private sectors. Major factors in increasing costs are animal safety studies and large-scale clinical trials.

Although efforts in contraceptive development have been modest in the pharmaceutical industry since the mid-1960s, there has recently been some renewed interest. As new antifertility agents become available, characterized by different mechanisms of action and different administrative schedules from those for the current oral contraceptives, less costly and less extensive animal toxicology requirements can be anticipated. As indicated by table 1, the preclinical requirements for contraceptive agents are currently far more rigorous than those for other drugs. On one hand, because nonhuman primates are no longer imported and domestic breeding programs are not yet able to supply enough animals to meet requirements, the time needed to complete future studies may of necessity become extended. On the other hand, serious questions have been raised recently about the importance of information obtained from the use of dogs in preclinical safety studies; this issue remains to be resolved.

As new information on existing antifertility methods accumulates, additional testing for specific effects is necessary. It is now known, for example, that progestins used in OCs influence blood lipids and that a similar situation may exist with respect to the estrogens.[67] Although information concerning effects on blood lipids may be closely related to drug safety issues and should be available for a new contraceptive drug, all animal and clinical studies that incorporate additional testing continue to increase the costs of evaluation.

Patent Rights

As a matter of law, the Government retains the rights to inventions developed in the course of Government-supported research. The rights to inventions can be assigned to the inventor; however, assignments have been traditionally made on a case-by-case basis. Academic and nonprofit institutions are in a position to negotiate Institutional Patent Agreements (IPAs) which allocate rights to inventions to individuals working in those institutions. The Department of Health and Human Services granted the NIH such a patent exemption for contractors in the cancer chemotherapy development program. This was not the case in the contraceptive development program. This exclusion has appeared to limit industrial participation. Bills that have been introduced in Congress to simplify the assignment of patent rights to nonprofit institutions and, in the case of industry, to

permit the granting of exclusive licenses may provide a stimulus for interaction and cooperation between Government-supported programs and industry.[68]

Liability Insurance

When a drug or device is tested on humans, there is a risk of legal action if there is a health-threatening reaction to the product. Although the pharmaceutical industry is covered by a variety of product liability policies, it has not been willing to undertake the sale of some products that carry a substantial risk factor. In the swine flu vaccination program, for example, specific indemnification legislation had to be passed in order for vaccine manufacturers to agree to participate.[69] This concern extends to most universities and research institutes that do not carry product liability insurance. Such insurance is difficult to obtain and, when it can be purchased, is expensive. The cost of insuring 10 subjects in a recent phase I clinical trial of a drug delivery device, for example, was $30,000.

Potential risks in Government-sponsored projects are recognized in procurement regulations, and in order to cope with financial losses that may result from injury, a contractor may be protected through the so-called "Liability to Third Persons" clause.[70] Although insertion of the clause into a contract would permit the contractor to recover from the Government the costs and expenses arising from litigation, the Department of Health and Human Services cautions against its use because of its complex legal nature. Steps are being taken to resolve this issue.

Summary

The recommended activities of research in contraceptive development range from laboratory investigations to clinical trials. The number of ongoing clinical trials as well as those projected has grown steadily.

Although new methods of regulating fertility will not in themselves resolve the problems of unplanned pregnancies, they do help couples in making a choice.

There is no question that the availability of a wider choice of contraceptive methods would help family planning services with their mission. The cost-benefit ratio of effective family planning is exceedingly high, and new products or approaches for effectively regulating fertility can reach a large segment of the population.

There are several approaches that a product development program can adopt. One would be to fund only initial research that more or less defines the feasibility of a product. Based on these findings, every attempt would then be made to spin off future developments to the private sector. This is a rational, cost-saving approach that has worked for some products. The other approach is to combine initial testing with all other phases of product development.

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